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(54) Benzazepine and benzoxazepine derivatives.

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EP-A-0 009 284
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DE-A-1 695 556
DE-A-1 795 728
DE-A-2 362 539
DE-A-2 441 261
DE-A-3 324 532

CHEMICAL ABSTRACTS, vol. 87, no. 7, August 15, 1977, Columbus, Ohio, USA V.M. DIXIT et al. "Agents acting on the chentral nervous system: Part XXV 2-substituted

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1,2,3,4,6,7,8,12b-octahydropyrazino (2,1-a) (2)benzapines page 466, column 2, abstract-no. 53 214a

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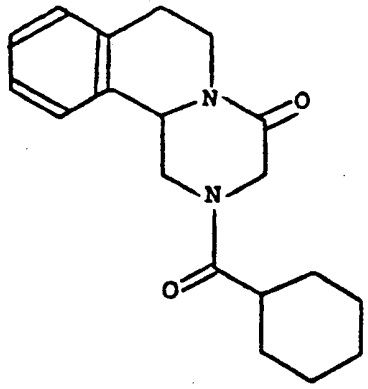
Descripti n

The present invention r lates to nov l benzazepine d rivatives having anthelmintic activity, t pharmaceutical formulati ns containing them and to their use in human or veterinary medicine.

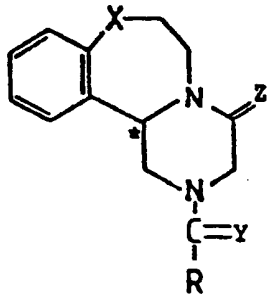
The compound praziquantel, which is 2-cyclohexylcarbonyl [1,2,3,6,7,11b] hexahydro-4H-pyrazino [2,1-a] isoquinolin-4-one, is a known compound having anthelmintic activity. Praziquantel has the structure (A):



(A)

Praziquantel and related pyrazino-isoquinoline derivatives are described in DE—A—1 795 728, DE—A—24 41 261, and DE—A—23 62 539.

We have now found a group of compounds having some of the structural features of praziquantel, but also having structural differences, which have useful anthelmintic activity, particularly against tapeworm. According to the present invention there is provided a compound of formula (I):



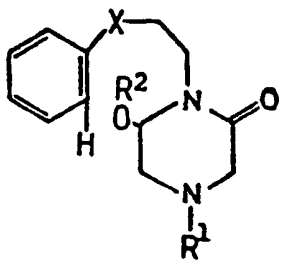
(I)

in which R is phenyl optionally substituted with one or more moieties selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino, mono-or-di-C_{1-6} alkylamino, and hydroxy; C_{3-8} cycloalkyl; C_{5-8} cycloalkenyl; C_{1-8} alkyl which may be straight or branched; C_{2-8} alkenyl which may be straight or branched; a 5- or 6-membered saturated or unsaturated heterocyclyl group containing one or more hetero-atoms selected from oxygen, sulphur and nitrogen; or phenyl C_{1-4} alkyl in which the phenyl group is optionally substituted with one or more moieties selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino, mono-or-di-C_{1-6} alkylamino, and hydroxy; each of Y and Z, which may be the same or different, is oxygen or sulphur; and X is $—CH_2—$ or oxygen.

Compounds of formula (I) have an asymmetric carbon atom marked by an asterisk in formula (I) and may therefore exist in at least two stereoisomeric forms. The present invention encompasses all isomers of the compounds of formula (I) whether pure or admixed with other isomers in any proportion.

A preferred R group is cyclohexyl.

Compounds of formula (I) may be produced by cyclising a compound of formula (II):



(II)

in which X is as defined in formula (I),

R^1 is hydrogen, a protecting group or a group

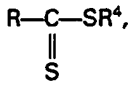
wherein R and Y are as defined in formula (I) and R^2 is C_{1-3} alkyl or hydrogen, and, when R^1 is a protecting group, removing the protecting group and replacing it with a group

and, when R^1 is hydrogen, replacing it with a group

and optionally thereafter converting the compound of formula (I) thus formed, wherein Z is oxygen, to a compound of formula (I) wherein Z is sulphur, by treatment with a thionation reagent.

A preferred thionation reagent is Lawessons reagent. In the above process, replacement of the group

in which Y is sulphur, may be carried out by treatment with a dithioic ester of formula



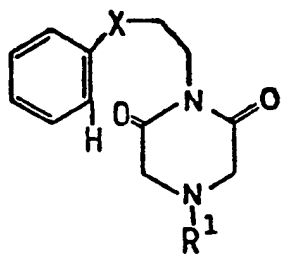
wherein R is hereinbefore defined and R^4 is C_{1-6} alkyl.

As used herein the term 'protecting group' refers to a group which is stable under the cyclisation reaction conditions but which may readily be removed after the cyclisation is complete. A typical example of such a protecting group is benzyl, which may be removed by catalytic hydrogenation, for instance using a palladium catalyst in a suitable solvent.

Examples of R^2 are C_{1-3} alkyl and hydrogen, preferably hydrogen.

Compounds of formula (II) may be cyclised by treatment with an acid catalyst, and conveniently an acid such as polyphosphoric acid may be used. The reaction may be conducted at elevated temperature, such as 100°C or greater, for instance at about 180°C. Alternatively, concentrated sulphuric acid may be used, in which case the reaction is carried out at a lower temperature, for example from −10°C to 40°C.

Compounds of formula (II) wherein R^2 is hydrogen may be produced by reducing the corresponding imide of formula (III):



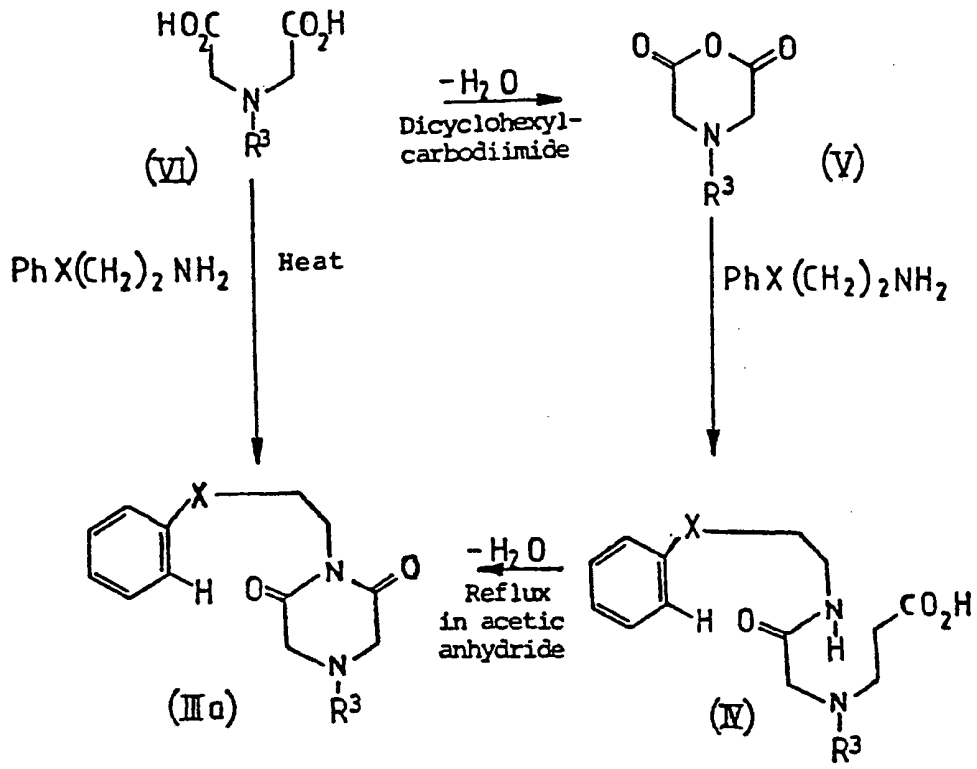
(III)

wh rein X, and R^1 are as h reinbefore defined. The reduction is effected using a suitable hydride reducing agent, such as sodium borohydride in a suitable solvent such as a lower alkanol, pref rably ethanol.

Compounds of formula (II) wherein R^2 is alkyl may be produc d by conventional methods, such as those outlined in the papers of W. Speckamp *et al* (for exampl , see Tetrahedron *31*, 1437, 1975).

Compounds of formula (III) may be produced according to Scheme I, using conventional reagents, such as those shown in th scheme.

Schem I



In Scheme I R^3 is a protecting group or a group

in which Y is as hereinbefore defined, and X is as hereinbefore defined.

Compounds of formula (III) wherein R^1 is hydrogen are produced by removing the protecting group from a compound of formula (IIIa). Further details of the reaction conditions appear in the Examples below.

Compounds of formula (I) have anthelmintic activity especially against tapeworm such as *Taenia taeniaeformis* and *Dipylidium caninum.*

Accordingly the present invention also provides a compound of formula (I), as hereinbefore defined, for use in the treatment of the human or non-human animal body, especially for treating helminthiasis and particularly for treating tapeworm infestations, of domestic and farm animals.

The present invention also provides a pharmaceutical or veterinary composition comprising a compound of formula (I) and a pharmaceutically or veterinarily acceptable carrier therefor.

Suitably the compositions consist of sufficient material to provide a dose of from 0.01 to 250 mg of active ingredient per kg of animal body weight per dose, more suitably 0.1 to 50 mg/kg per dose.

It will be appreciated that, in some cases, it will be advisable to repeat the dosing of the infected or potentially infected human or non-human animal with a compound of formula (I) according to conventional dosage regimes normally used with anthelmintics.

The following Examples illustrate the invention.

Examples XI to X6 and X7 to XII illustrate the preparation of intermediate compounds, while Examples 1 to 35 illustrate the preparation of compounds of the invention. Example X7 illustrates the resolution of a compound of the invention.

Example 1

2-(Cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazepine

Cyclohexanoyl chloride (0.34 g) was added to a solution of 4-oxo-1,2,3,4,6,7,8,12*b*-octahydropyrazino[2,1-*a*][2]benzazepine (0.5 g) in chloroform (20 ml, ethanol-free) maintained at 0°C and triethylamine (0.26 g) added. Th mixtur was maintained at 0°C for 30 min then at room temperature for 5h. The solution was wash d with, first, dilute hydrochloric acid and s condly with s dium bicarbonate solution. The chloroform solution was dried ($MgSO_4$) and evaporated. The residue was recrystallized from

chloroform/40—60°C petroleum ether to give white crystals of the title compound (0.48 g, 64%) m.p. 187—90°C.
Found:— C: 73.2, H: 7.7, N: 8.4%
$C_{20}H_{26}N_2O_2$ requries C: 73.6, H: 8.0, N: 8.6%

Example XI

1-(3-Phenylpropyl)-4-benzyl-2,6-piperazinedione

3-Phenyl-1-propylamine (3.63 g) and N-benzyliminodiacetic acid (6.0 g) was mixed and heated to 200°C under a nitrogen atmosphere. The mixture was stirred at this temperature for 1h, cooled and purified by column chromatography (SiO_2, 40—60°C petroleum ether/chloroform) to give the title material as a pale orange liquid (5.53 g, 64%).

Example X2

1-(3-Phenylpropyl)-4-benzyl-2-hydroxy-6-oxopiperazine

Saturated aqueous sodium bicarbonate solution (20 ml) was added to a solution of 1-(3-phenylpropyl)-4-benzyl-2,6-piperazinedione (5.35 g) in ethanol (170 ml) at 5°C and sodium borohydride (1.23 g) added portionwise to the resulting mixture at 5°C over a period of 2h. The mixture was stirred for a further 1h at 5°C and the solvent removed *in vacuo*. Water (50 ml) was added, and the mixture extracted with dichloromethane (3 × 50 ml), the extracts washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave the title compound as a white solid (4.36 g, 81%).

Example X3

2-Benzyl-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazepine

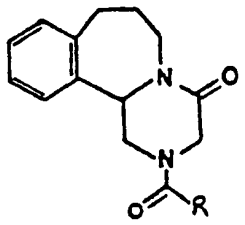
1-(3-Phenylpropyl)-4-benzyl-2-hydroxy-6-oxopiperazine (2.6 g) and polyphosphoric acid (53 g) were mixed, heated at 180°C and maintained at this temperature for ¾h. The mixture was cooled to 60°C and water (200 ml) added. The mixture was cooled, basified with sodium hydroxide solution, and extracted with chloroform (3 × 50 ml). The solvent was evaporated and the product crystallised from diethyl ether to give the title compound (0.78 g, 32%) m.p. 125—8°C.

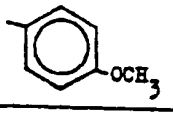
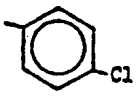
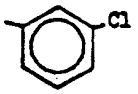
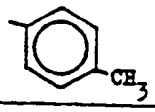
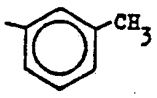
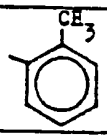
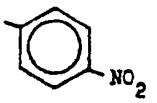
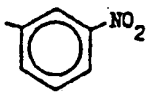
Example X4

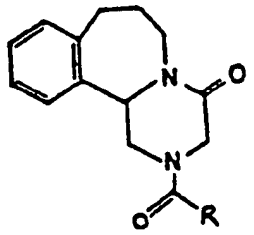
4-Oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazepine

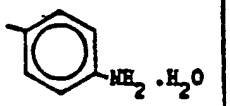
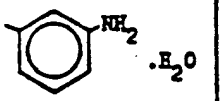
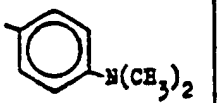
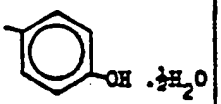
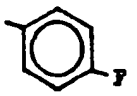
Hydrogenolysis of 2-benzyl-4-oxo-1,2,3,4,6,7,8,12*b*-octahydropyrazino[2,1-*a*][2]benzazepine (1.39 g) in solution in ethanol (40 ml) by treatment with hydrogen at 45°C and atmospheric pressure in the presence of a palladium on charcoal catalyst (0.3 g) gave the title compound (0.6 g, 61%).

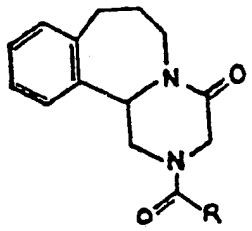
The following tabulated Examples 2 to 26 can be made in analogous fashion to the preparation of Example 1.

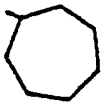
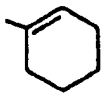
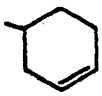
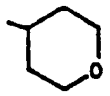
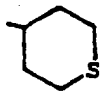


Example No.	R	m.p. °C	Microanalytical Data/Mass Spectral Data							
			Calculated				Found			
			C	H	N		C	H	N	
2		166-167	Theoretical m/e 320.1525				Observed m/e 320.1538			
3		167-171	71.98	6.33	7.99		72.06	6.47	7.78	
4		184-186	67.70	5.40	7.89		67.37	5.57	7.83	
5		148-151	67.70	5.40	7.89		67.27	5.37	7.88	
6		179-181	75.42	6.63	8.38		75.02	6.51	8.21	
7		152.5-153.0	75.42	6.63	8.38		75.72	6.67	8.36	
8		127-128	75.42	6.63	8.38		75.42	6.67	8.34	
9		217-218	65.74	5.24	11.50		65.10	5.43	11.43	
10		170-171	65.74	5.24	11.50		65.54	5.03	11.43	



Example No.	R	m.p. °C	Microanalytical Data/Mass Spectral Data							
			Calculated				Found			
			C	H	N	Cl	C	H	N	Cl
11		217-218	67.97	6.56	11.89		67.76	6.44	11.43	
12		98-101	67.97	6.56	11.89		67.79	6.35	11.68	
13		197-198	72.70	6.93	11.56		72.46	6.95	11.37	
14		190-195	69.55	6.13	8.11		69.63	6.03	7.82	
15		168-169	70.99	5.66	8.28		70.33	5.62	8.12	
16	$-CH_3$	137-139	69.72	7.02	10.84		69.49	6.83	10.72	
17		162-163	71.30	7.74	9.78		71.18	7.87	9.73	
18	$-C_5H_{11}(n)$	91-92	72.58	8.34	8.91		72.45	8.49	8.80	
19		157-159	72.46	7.43	9.39		72.51	7.55	9.06	



Example No.	R	m.p. °C	Microanalytical Data/Mass Spectral Data							
			Calculated				Found			
			C	H	N	S	C	H	N	S
20		154-155	73.05	7.74	8.97		72.31	7.43	8.88	
21		160-165	74.08	8.29	8.23		74.27	8.30	8.14	
22		149-150	74.04	7.46	8.63		73.97	7.46	8.61	
23		183-185	74.04	7.46	8.63		74.11	7.54	8.55	
24		214-215	Theoretical m/e 328.1787				Observed m/e 328.1795			
25		164-165	66.25	7.02	8.13	9.31	66.49	7.05	9.09	8.98
26		170-171	71.01	5.96	13.07		71.37	6.06	12.98	

Example X5

2-(Triph nylmethyl)-4-ox -1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazepine

Triphenylmethyl chlorid (0.47 g) was added to a mixture f 4-ox -1,2,3,4,6,7,8,12*b*-octahydropyrazino[2,1-a][2]benzazepine (0.31 g) and triethylamine (0.25 ml) in chloroform (25 ml, ethanol-free) at 0°. Th mixture was maintained at 0° for 30 min then at room temperature for 90 min. The solution was washed with saturated sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (SiO_2, Et_2O) to give the title compound (0.66 g, 100%) as a white powder.

Example X6

4-Thioxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazepine

A mixture of 2-(triphenylmethyl)-4-oxo-1,2,3,4,6,7,8,12*b*-octahydropyrazino[2,1-a][2]benzazepine (0.66 g) and Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide) (0.29 g) in HMPA (10 ml) was heated to 80° under a nitrogen atmosphere. The mixture was stirred at this temperature for 3 hr, cooled and partitioned between water and diethyl ether. The organic layer was washed with water and evaporated to a yellow foam. This residue was dissolved in acetone (20 ml), cooled to 0° and concentrated hydrochloric acid (0.5 ml) added. After stirring at room temperature for 30 min the mixture was evaporated and the residue partitioned between dilute hydrochloric acid and chloroform. The aqueous fraction was basified with sodium carbonate and extracted with chloroform. This chloroform fraction was washed with brine, dried (K_2CO_3) and evaporated to give the title compound as a white solid.

Example 27

2-(Cyclohexylcarbonyl)-4-thioxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazepine

Cyclohexanoyl chloride (0.16 g) was added to a mixture of 4-thioxo-1,2,3,4,6,7,8,12*b*-octahydropyrazino[2,1-a][2]benzazepine (0.24 g) and triethylamine (0.25 ml) in chloroform (20 ml, ethanol-free) at 0°. The mixture was maintained at 0° for 30 min then at room temperature for 5 hr. The solution was washed with, first, dilute hydrochloric acid, and secondly with sodium bicarbonate solution. The chloroform solution was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (SiO_2, Et_2O) and recrystallised from dichloromethane/40—60°C petroleum ether to give white crystals of the title compound (55 mg, 16%) m.p. 150—151°C.

Found: C: 70.4, H: 7.8, N: 8.1, S; 8.8%

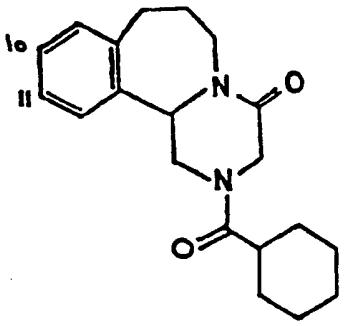
$C_{20}H_{26}N_2OS$ requires: C: 70.1, H: 7.8, N: 8.2, S: 9.3%

Example 28

2-(Cyclohexylcarbonyl)-4-thioxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazepine

A mixture of 2-(cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12*b*-octahydropyrazino[2,1-a][2]benzazepine (0.30 g) and Lawesson's reagent (0.19 g) in HMPA (4 ml) was heated to 80° under a nitrogen atmosphere. The mixture was stirred at this temperature for 3 hr, cooled and poured into water. This was extracted with diethyl ether. The organic layer was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (SiO_2, Et_2O) and recrystallisation (CH_2Cl_2/40—60 petroleum ether) to give white crystals of the title compound (0.13 g, 41%) m.p. 150—151°C.

By use of suitably substituted 3-phenylpropylamines in Examples X1 to X4, substituted 4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2] benzazepines were obtained which, on reaction with cyclohexanoyl chloride according to the procedure in Example 1, afforded the following substituted 2-(cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazepines:—



Example	Substituent	Accurate Mass Measurement (m/e)	
		Found	Calculated
29	11-CH_3	340.2152 [M$^+$]	340.2150 ($C_{21}H_{26}N_2O_2$)
30	10,11-diOCH_3	386.2202 [M$^+$]	386.2205 ($C_{22}H_{30}N_2O_4$)

Example 31

Nitration of 2-(cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazepine

2-(Cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazepine (600 mg, 1.8 mmol) was dissolved in concentrated sulphuric acid (7 ml) and concentrated nitric acid (4 ml) with cooling. The solution was heated at 35°C for 2 hours, poured into water (100 ml) and extracted with $CHCl_3$ (2 x 50 ml). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a mixture of the 10- and 11-mono-nitrated products which were separated by preparative HPLC [Ultrasil® ODS 10 µ, 25 cm x 10 mm, MeOH:H_2O (7:3), 1 ml/min]. Retention times 8.3 min and 9.2 min.

Example X7

Resolution of 2H-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino (2,1-a) (2) benzazepine

(±) 2H-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino (2,1-a) (2) benzazepine (3.2 g, 0.0148 mol) was dissolved in methanol (35 ml) and a solution of (−) tartaric acid (2.45 g, 0.0163 mol) in methanol (140 ml) added.

The mixture was heated on a steam bath, filtered whilst hot, and allowed to cool. White crystals were deposited, and these were filtered, and recrystalised from methanol (250 ml) to give the (−) tartarate salt of (−) 2H-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino (2,1-a) (2) benzazepine $(\alpha)_D^{22}$ −149° (H_2O).

A solution of this salt in water gave, upon basification with ammonium hydroxide and extraction with chloroform, the free base (−) 2H-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino (2,1-a) (2) benzazepine as a white solid $(\alpha)_D^{22}$ − 221° (CH_3OH).

Similarly, using (+) tartaric acid in place of (−) tartaric acid was obtained:—

(+) 2H-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino (2,1-a) (2) benzazepine

(+) tartrate $(\alpha)_D^{22}$ +153° (H_2O).

Found C; 55.7, H; 6.1, N; 7.4%

$C_{17}H_{22}N_2O_7$ requires C; 55.7; H; 6.0, N; 7.6%

and (+) 2H-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino (2,1-a) (2) benzazepine free base $(\alpha)_D^{22}$ +212° (CH_3OH).

Example 32

(+) 2-(cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino (2,1-a) (2) benzazepine

The title compound was obtained by the method of example I using (+) 2H-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino (2,1-a) (2) benzazepine in place of the racemic amine. The product was purified by column chromatography (Si/$CHCl_3$). $(\alpha)_D^{22}$ +41° (CH_3OH).

Example 33

(−) 2-(cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino (2,1-a) (2) benzazepine

The title compound was obtained as a white solid by the procedure outlin d in example I using (−) 2H-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino (2,1-a) (2) benzazepine in place of th racemic amin . The product was purifi d by column chromatography (Si/$CHCl_3$). $(\alpha)_D^{22}$ −42° (CH_3OH).

Exampl 34

2-(Cyclohexylthiocarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazepin

Methyl cyclohexanecarbodithioate (0.24 g) was added to a solution of 4-oxo-1,2,3,4,6,7,8,12*b*-octahydropyrazino[2,1-a][2]benzaz pine (0.3 g) in dimethylformamide (5 ml). The mixture was refluxed for 4 h, cooled and poured into wat r. This was extracted with diethyl ether; the ether solution was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (SiO_2, diethyl ether).
m/e observed: 342.1770
$C_{20}H_{26}N_2OS$ requires 342.1766

Example 35

2-(Cyclohexylcarbonyl)-4-oxo-1,2,3,6,7,12b-hexahydropyrazino [1,2-d] [1,4]benzoxazepine

4-Oxo-1,2,3,6,7,12*b*-hexahydropyrazino [1,2-d] [1,4] benzoxazepine (0.9 g) and triethylamine (1 g) were dissolved in dichloromethane (20 ml), cooled in ice and cyclohexanoyl chloride (0.7 g, 1.1 equiv.) added. The mixture was stirred at room temperature for 3 h, then washed with dilute aqueous hydrochloric acid, followed by dilute aqueous ammonia solution. Evaporation of the dichloromethane gave an oil which was purified by column chromatography (SiO_2/chloroform) and crystallised from ether/40°—60° petroleum ether to give white crystals of the title compound m.p. 92—3°;
found: C, 69.53; H, 7.40; N, 8.54%
$C_{19}H_{24}N_2O_3$ requires C, 69.49; H, 7.37; N, 8.53%.

Example X8

1-(2-Phenoxyethyl)-4-benzyl-2,6-piperazinedione

2-Phenoxyethylamine (1.37 g) and N-benzyliminodiacetic acid (2.23 g) were mixed and heated to 225°, and maintained at this temperature for 15 min. After cooling, chloroform was added and the product purified by column chromatography (SiO_2/$CHCl_3$) to give the title compound as a reddish oil (2.1 g).

Example X9

1-(2-Phenoxyethyl)-4-benzyl-2-hydroxy-6-oxopiperazine

1-(2-Phenoxyethyl)-4-benzyl-2,6-piperazinedione (2.24 g) in ethanol (60 ml) and saturated sodium bicarbonate solution (15 ml) was cooled to 5° and sodium borohydride (0.4 g) added. The mixture was stirred at 5° for 1 h, water (150 ml) added and the mixture extracted with chloroform (3×75 ml). Evaporation of the chloroform gave the title compound as an off-white solid (2.1 g).

Example X10

2-Benzyl-4-oxo-1,2,3,6,7,12b-hexahydropyrazino [1,2-d] [1,4] benzoxazepine

1-(2-Phenoxyethyl)-4-benzyl-2-hydroxy-6-oxopiperazine (4 g) was added to concentrated sulphuric acid (50 ml) at 0—10° and the mixture stirred for 30 min. The resulting solution was poured onto ice, basified with NH_4OH and extracted with chloroform to give the title compound as a pale oil (2 g).

Example X11

4-Oxo-1,2,3,6,7,12b-hexahydropyrazino [1,2-d][1,4]benzoxazepine

Hydrogenation of 2-benzyl-4-oxo-1,2,3,6,7,12b-hexahydropyrazino[1,2-d] [1,4]benzoxazepine in 90% acetic acid over a palladium on charcoal catalyst (5%) at 50°C and a pressure of $400KN_m^{-2}$ of hydrogen gave, after basification and extraction, the title compound.

Pharmacological data

A cat infected with *Taenia Taeniaeformis* and *Dipylidium caninum* was treated with 2-(cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12*b*-octahydropyrazino-[2,1-a][2]benzazepine at 30 mg/kg p.o. This treatment completely removed the tapeworm infections.

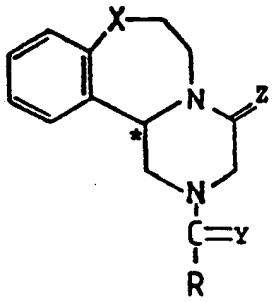
The following compounds were administered orally to cats infected with *Dipylidium caninum* and/or *Taenia taeniaeformis* and the following activities noted.

Compound of Example No.	Dose mg/kg p.o.	Activity %	
		Taenia	Dipylidium
1	1	100	100
20	1	100	100
21	5	100	NI
22	5	100	NI
35	5	100	100

NI = Not infected

Claims

1. A compound of formula (I):



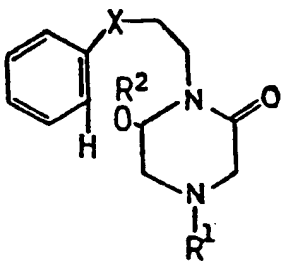
(I)

in which R is phenyl optionally substituted with one or more moieties selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino, mono-or-di-C_{1-6} alkylamino, and hydroxy; C_{3-8} cycloalkyl; C_{5-8} cycloalkenyl; C_{1-8} alkyl which may be straight or branched; C_{2-8} alkenyl which may be straight or branched; a 5- or 6-membered saturated or unsaturated heterocyclyl group containing one or more hetero-atoms selected from oxygen, sulphur and nitrogen; or phenyl C_{1-4} alkyl in which the phenyl group is optionally substituted with one or more moieties selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino, mono-or-di-C_{1-6} alkylamino, and hydroxy; each of Y and Z, which may be the same or different, is oxygen or sulphur; and X is —CH_2— or oxygen.

2. A compound as claimed in claim 1, wherein R is cyclohexyl.

3. A compound as claimed in claim 2, being 2-(cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazepine.

4. A process for the preparation of a compound of formula (I), which process comprises cyclising a compound of formula (II):



(II)

in which X is as defined in claim 1

R^1 is hydrogen, a prot cting group or a group

wherein R and Y are as defined in claim 1 and R^2 is C_{1-3} alkyl or hydrogen, and, when R^1 is a protecting group, removing the protecting group and replacing it with a group

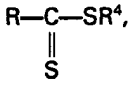
and, when R^1 is hydrogen, replacing it with a group

and optionally thereafter converting the compound of formula (I) thus formed, wherein Z is oxygen, to a compound of formula (I) wherein Z is sulphur, by treatment with a thionation reagent.

5. A process as claimed in claim 4, wherein the thionation agent is Lawesson's reagent.

6. A process as claimed in claim 4 or claim 5, wherein replacement of the group

in which Y is sulphur, may be carried out by treatment with a dithioic ester of formula



wherein R is hereinbefore defined in claim 1 and R^4 is C_{1-6} alkyl.

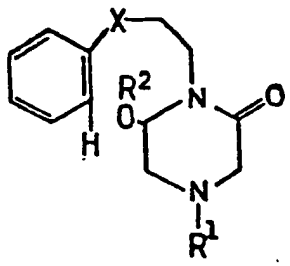
7. A process as claimed in any one of claims 4 to 6, wherein R^2 is hydrogen.

8. A compound of formula (I), as defined in claim 1, for use in the treatment of the human or non-human animal body for treating helminthiasis.

9. A compound of formula (I), as defined in claim 1, for use in the treatment of tapeworm infestations of domestic and farm animals.

10. A pharmaceutical or veterinary composition comprising a compound of formula (I) as defined in claim 1 and a pharmaceutically or veterinarily acceptable carrier therefor.

11. A compound of formula (II):

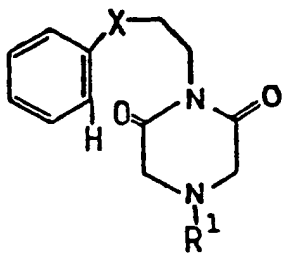


(II)

in which X is $—CH_2—$ or oxygen, R^1 is hydrogen, a protecting group or a group

wherein R and Y are defined with resp ct to the compound of formula (I) as defined in Claim 1, and R^2 is C_{1-3} alkyl or hydrogen.

12. A compound of formula (III):

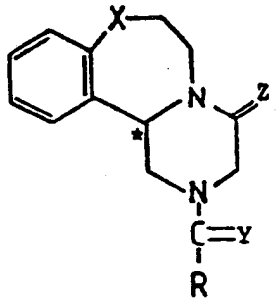


(III)

wherein X and R^1 are defined with respect to the compound of formula (II) as defined in Claim 11.

Patentansprüche

1. Eine Verbindung der Formel (I):



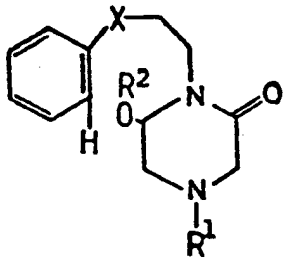
(I)

in welcher R Phenyl, gegebenenfalls substituiert mit einer oder mehreren Gruppe(n), ausgewählt aus Halogen, C_{1-6}-Alkyl, C_{1-6}-Alkoxy, Nitro, Amino, mono- oder di-C_{1-6}-Alkylamino und Hydroxy; C_{3-8}-Cycloalkyl; C_{5-8}-Cycloalkenyl; C_{1-8}-Alkyl, welches geradkettig oder verzweigt sein kann; C_{2-8}-Alkenyl, welches geradkettig oder verzweigt sein kann; eine 5- oder 6-gliedrige gesättigte oder ungesättigte Heterocyclylgruppe, enthaltend ein oder mehrere Heteroatom(e) ausgewählt aus Sauerstoff, Schwefel und Stickstoff; oder Phenyl-C_{1-4}-Alkyl, in welchem die Phenylgruppe gegebenenfalls substituiert ist mit einer oder mehreren Gruppe(n), ausgewählt aus Halogen, C_{1-6}-Alkyl, C_{1-6}-Alkoxy, Nitro, Amino, mono- oder di-C_{1-6}-Alkylamino, und Hydroxy ist; Y und Z, welche gleich oder verschieden sein können, jeweils Sauerstoff oder Schwefel darstellen; und X eine Gruppe —CH_2— oder Sauerstoff ist.

2. Eine Verbindung wie in Anspruch 1 beansprucht, in welcher R Cyclohexyl ist.

3. Eine Verbindung wie in Anspruch 2 beansprucht, nämlich ein 2-(Cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazepin.

4. Ein Verfahren zur Herstellung einer Verbindung der Formel (I), welches Verfahren das Cyklisieren einer Verbindung der Formel (II):



(II)

in welcher X wie in Anspruch 1 definiert ist, R^1 Wasserstoff, eine Schutzgruppe oder eine Gruppe

ist, in welcher R und Y wie in Anspruch 1 definiert ist, und R^2 C_{1-3}-Alkyl oder Wasserstoff bedeutet, und, wenn R^1 eine Schutzgruppe ist, das Entfernen der Schutzgruppe und Ersetzen derselben durch eine Gruppe

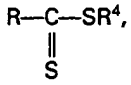
wenn R^1 Wasserstoff ist, Ersetzen desselben durch eine Gruppe

und, gegebenenfalls anschließend das Umwandeln der so gebildeten Verbindung der Formel (I), in welcher Z Sauerstoff ist, in eine Verbindung der Formel (I), in welcher Z Schwefel ist, durch Behandlung mit einem Thionisierungsreagens umfaßt.

5. Ein Verfahren wie in Anspruch 4 beansprucht, in welchem das Thionisierungsreagens Lawesson's Reagens ist.

6. Ein Verfahren wie in Anspruch 4 oder 5 beansprucht, in welchem das Ersetzen der Gruppe

in welcher Y Schwefel ist, durch Behandlung mit einem Dithioester der Formel



in welcher R wie oben in Anspruch 1 definiert ist, und R^4 C_{1-6}-Alkyl ist, durchgeführt werden kann.

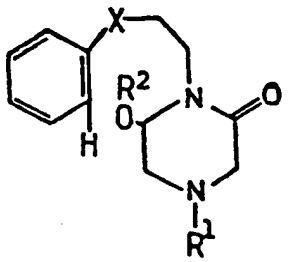
7. Ein Verfahren wie in einem der Ansprüche 4 bis 6 beansprucht, in welchem R^2 Wasserstoff ist.

8. Eine Verbindung der Formel (I), wie in Anspruch 1 definiert, zur Verwendung bei der Behandlung des menschlichen oder tierischen Körpers in der Therapie von Helminthiasis.

9. Eine Verbindung der Formel (I), wie in Anspruch 1 definiert, zur Verwendung bei der Behandlung von Bandwurmbefall bei Haustieren und Vieh.

10. Eine pharmazeutische oder veterinärmedizinische Zusammensetzung, umfassend eine Verbindung der Formel (I) wie in Anspruch 1 definiert und einen pharmazeutisch oder veterinär-medizinisch verträglichen Träger dafür.

11. Eine Verbindung der Formel (II):

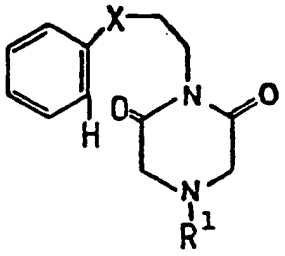


(II)

in welcher X eine Gruppe $—CH_2—$ oder Sauerstoff ist, R^1 Wasserstoff, eine Schutzgruppe oder eine Gruppe

ist, in welcher R und Y wie in bezug auf die Verbindung der Formel (I), wie in Anspruch 1 angegeben, definiert sind, und R^2 C_{1-3}-Alkyl oder Wasserstoff ist.

12. Eine Verbindung der Formel (III):

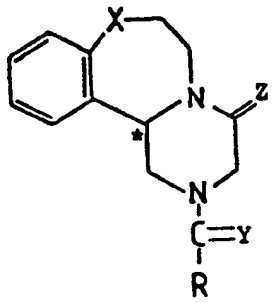


(III)

in welcher X und R^1 wie in bezug auf di Verbindung der Formel (II), wie in Anspruch 11 angegeben, definiert sind.

Revendications

1. Composé de formule (I):



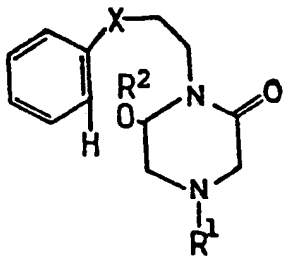
(I)

dans laquelle R est un groupe phényle éventuellement substitué avec une ou plusieurs parties choisies parmi un atome d'halogène, un groupe alcoyle en C_{1-6}, alcoxy en C_{1-6}, nitro, amino, mono- ou di-alcoyl(C_{1-6})amino et hydroxy; cycloalcoyle en C_{3-8} cycloalcènyle en C_{5-8}; alcoyle en C_{1-8} à chaîne droite ou ramifiée; alcényle en C_{2-8} à chaîne droite ou ramifiée; un groupe hétérocyclyle saturé ou insaturé à 5 ou 6 chaînons contenant un ou plusieurs hétéroatomes choisis parmi des atomes d'oxygène, de soufre et d'azote; ou phénylalcoyle en C_{1-4} dont le cycle phényle est éventuellement substitué avec une ou plusieurs parties choisies parmi un atome d'halogène, un groupe alcoyle en C_{1-6}, alcoxy en C_{1-6}, nitro, amino, mono- ou di-alcoyl(C_{1-6})amino et hydroxy; chacun des Y et Z, qui peuvent être identiques ou différents est un atome d'oxygène ou de soufre; et X est un radical $—CH_2—$ ou un atome d'oxygène.

2. Composé suivant la revendication 1, caractérisé en ce que R est un groupe cyclohexyle.

3. Composé suivant la revendication 2, caractérisé en ce qu'il s'agit de la 2-(cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-a][2]benzazépine.

4. Procédé pour la préparation d'un composé de formule (I), caractérisé en ce qu'il comprend la cyclisation d'un composé de formule (II):



(II)

dans laquelle X est tel que défini dans la revendication 1 R^1 est un atome d'hydrogène, un groupe protecteur ou un groupe

où R et Y sont tels que définis dans la revendication 1 et R^2 est un groupe alcoyle en C_{1-3} ou un atome d'hydrogène et, lorsque R^1 est un groupe protecteur, l'élimination du groupe protecteur et le remplacement de celui-ci par un groupe

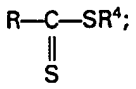
et, lorsque R^1 est un atome d'hydrogène, le remplacement de celui-ci par un groupe

et éventuellement ensuite, la conversion du composé de formule (I) ainsi formé, dans laquelle Z est un atome d'oxygène, en un composé de formule (I) dans laquelle Z est un atome de soufre, par traitement avec un réactif de thionation.

5. Procédé suivant la revendication 4, caractérisé en c que l'agent de thionation est un réactif de Lawesson.

6. Procédé suivant la rev ndication 4 ou la r vendication 5, caractérisé en ce que le remplacement du groupe

dans lequel Y est un atome de soufre, peut être effectué par traitement avec un ester dithioïque de formule



dans laquelle R est tel que défini plus haut dans la revendication 1 et R^4 est un groupe alcoyle en C_{1-6}.

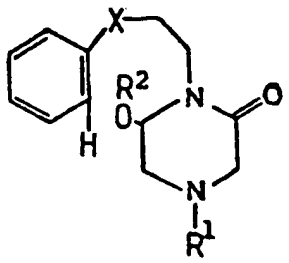
7. Procédé suivant l'une quelconque des revendications 4 à 6, caractérisé en ce que R^2 est un atome d'hydrogène.

8. Composé de formule (I) suivant la revendication 1, caractérisé en ce qu'il est utile dans le traitement de l'homme ou d'un animal non-humain pour traiter l'helminthiase.

9. Composé de formule (I) suivant la revendication 1, caractérisé en ce qu'il est utile dans le traitement des infestations de ténia chez des animaux domestiques et d'élevage.

10. Composition pharmaceutique ou vétérinaire caractérisée en ce qu'elle comprend un composé de formule (I) suivant la revendication 1 et un support acceptable du point de vue pharmaceutique ou vétérinaire.

11. Composé caractérisé par la formule (II):

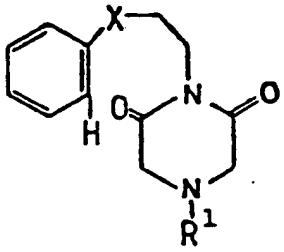


(II)

dans laquelle X est un radical $—CH_2—$ ou un atome d'oxygène, R^1 est un atome d'hydrogène, un groupe protecteur ou un groupe

où R et Y sont tels que définis à propos du composé de formule (I) suivant la revendication 1, et R^2 est un groupe alcoyle en C_{1-3} ou un atome d'hydrogène.

12. Composé caractérisé par la formule (III):



(III)

dans laquelle X et R^1 sont tels que définis à propos du composé de formule (II) suivant la r vendication 11.